

Endothelial Dysfunction And Secondary Hyperparathyroidism in End Stage Renal Disease(ESRD)

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Abstract

Background Cardiovascular disease is the leading cause of morbidity and mortality in patients with chronic kidney disease. Endothelial dysfunction represents an obligatory, prodromal phase in the atherosclerosis process. Secondary hyperparathyroidism is an integral component of the uremic syndrome .

Aim: is to study endothelial dysfunction in patients with uremia in relation to secondary hyperparathyroidism.

Patients and methods: Two groups of patients were studied: a group of 40 patients on regular hemodialysis 3times/week,4 hours/session , and a group of 30 patients with chronic kidney disease on conservative management. They were compared to 30 healthy age and sex matched normal controls. Measurement of flow-mediated (FMD) and nitroglycerine-induced vasodilatation (NMD) were done ,in addition to routine laboratory investigation including intact PTH assay.

Results: Both flow-mediated vasodilation($8.52\pm2.9\%$ in hemodialysis patients and $13.33\pm1.44\%$ in CKD patients) and flow-independent vasodilation (nitroglycerine mediated)($15.93\pm3.4\%$ in HD group and $17.06 \pm2.02\%$ in CKD) were compromised when compared to controls(FMD $16.02\pm 2.9\%$ and NMD $20.76\pm 4.3\%)(p<0.05)$.FMD was significantly compromised in HD versus CKD group ($p<0.05$)but this was not the case for NMD. Both FMD and NMD were significantly negatively correlated with serum creatinine and PTH .

Conclusion: Control of PTH levels in different stages of kidney disease may be part of the strategy to reduce the burden of atherosclerosis associated with CKD and PTH levels could be useful to identify patients at higher risk of future cardiovascular events

Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in patients with chronic kidney disease, being 10-20 fold higher in dialysis patients than in the general population and representing at least half of the 15-25% per year mortality rate .Cardiovascular events increase as the estimated glomerular filtration rate declines below 60 ml/min(Go *et al.*,2004).

Endothelial dysfunction represents an obligatory, prodromal phase in the atherosclerosis process (Zoccali, 2008). Assessment of endothelial dysfunction appears to be useful in the prediction of morbidity and mortality in cardiovascular risk groups (Cross, 2002).

Independently of the nature of the offending factor, the endothelial

dysfunction that results from the initial insult is characterized by increased adhesiveness of the endothelium to leukocytes and platelets and by the synthesis of vasoactive molecules, cytokines and procoagulant factors (Zoccali *et al.*,2003).

In renal failure, endothelial dysfunction and atherosclerosis are almost universal, as well as cardiovascular complications. Patients with end-stage renal disease (ESRD) are at additional risk for endothelial cell dysfunction because the uniform presence of hyperhomocysteinemia, accumulation of the endogenous inhibitor of nitric oxide(NO) synthase, asymmetric dimethylarginine (ADMA), anemia, oxidative stress(Stewart *et al.*, 2004) and exposure to bioincompatible

dialysis membranes and/or contaminated dialysis fluid (Zoccali *et al.*,2003).This facilitates cardiovascular complications in this cohort.

Hyperparathyroid condition affects endothelial cells (Baykan *et al.*,2007).

Recent data support the presence of subtle cardiovascular manifestations in mild hyperparathyroidism such as changes in endothelial function as well as increased vascular stiffness and perhaps diastolic dysfunction (Walker and Silverberg, 2008).

Endothelial dysfunction can be tested by a functional approach based on the forearm haemodynamic response to acetyl choline(a pharmacological stimulus impinging upon the enzyme NO synthase), or to ischemia [flow-mediated vasodilatation – (FMD) a physiological stimulus to the same enzyme]. Haemodynamic studies appear of particular value in clinical research, because altered endothelium-dependent vaso-regulatory control predicts cardiovascular complications in a variety of clinical settings (Zoccali, 2008).

Vascular calcification, wall hypertrophy, compromised reactivity and elasticity are frequently observed in connection with kidney disease and hyperparathyroidism and are associated with the emergence of cardiovascular complications. However ,it is not clear how parathyroid hormone (PTH),calcium and phosphorus interact to cause these alterations in dialysis patients (Block *et al.*,2004).

Aim:

Is to study endothelial dysfunction assessed by flow mediated dilatation (FMD) and nitroglycerine-induced vasodilatation (NMD) in patients with uremia on hemodialysis and on conservative management in relation to secondary hyperparathyroidism.

Patients and Methods

Two groups of patients were studied: a group of 40 patients on regular hemodialysis 3times/week,4 hours/session using bicarbonate solution and a group of 30 patients with chronic kidney disease on conservative management(stage 3 and 4).They were compared to 30 healthy age

and sex matched normal controls. Exclusion criteria were the following: diabetes, malignancy, liver disease, thyroid dysfunction, peripheral vascular disease, clinically evident cardiovascular disease , smoking, parathyroidectomy,use of oral contraceptives or lipid lowering agents (statins).

For all the patients a thorough history and physical examination was done and all medications were withdrawn 8 hours before testing including antihypertensives as angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptors blockers (ARBs) and calcium antagonists.

A fasting blood sample was withdrawn for all laboratory tests including serum creatinine, serum calcium, phosphorus, parathyroid hormone, fasting blood sugar, cholesterol, triglycerides, C reactive protein.

Intact parathyroid hormone level was assessed by radioimmunoassay method with normal range (12–65 pg/ml).

Measurement of flow-mediated and nitroglycerine-induced vasodilatation:

The studied subject had abstained from caffeine for 8 hours prior to the study and from strenuous physical activity for 24 hours before testing . Test was conducted in a temperature-controlled room with the subject in a supine position and the upper torso comfortably inclined. Uremic patients on dialysis were studied on the contralateral arm of the fistula or graft on a mid-week interdialysis day. The subjects were asked to lie quietly for at least 10min before the first scan. The brachial artery was visualized in a longitudinal scan 2–6 cm above the elbow using a 7.5 MHz linear array transducer software (Scanner 2000, Pie Medical Equipment) and the arm was kept in the same position throughout the study. A resting scan was obtained. Increased flow was then induced by the inflation of sphygmomanometer cuff placed around the forearm (distal to the scanned part of artery) to pressure of 200mmHg for 4.5min, followed by release. Cuff was deflated, and after 1min, the second or flow mediated dilatation (FMD) scan was obtained, which represents the endothelial-dependent dilation due to shear-induced endothelial-nitric oxide production. FMD is

expressed as the absolute or relative change in diameter from the baseline measurements. Endothelial independent dilation was measured by calculation of the vasodilator response 3 min after administration of 400 μ g of sublingual glycerol trinitrate when the vessel diameter had returned to baseline values. The percent diameter changes for FMD and nitrate-mediated dilation(NMD) was calculated in relation to its respective rest scan.. NMD was calculated accordingly as the maximum increase in artery diameter after sublingual application of glycerol trinitrate(Moens *et al.*, 2005).

Statistics

Statistical analysis was performed using the computer software SPSS (statistical Package of Social Science, 10, SPSS, Chicago, IL, USA). Data are expressed as mean \pm SD. Significance in the differences between means of the 2 groups and control was determined by one-way analysis of variance (ANOVA) and *post hoc* analysis by Bonferroni test. Pearson's correlations were used to define correlations. We used linear regression analysis to explore the variables affecting FMD. Statistical significance was assumed at $P<0.05$.

Results

Our study showed significant difference between both groups and control as regard blood urea nitrogen, creatinine,

low density lipoprotein, hemoglobin, hematocrit value. As regard the parameters of bone metabolism: serum phosphorus, calcium phosphorus product and parathyroid hormone showed significant difference between studied groups and control as well as a significant statistical difference between them. Serum calcium level failed to show any statistical difference between all groups (Table 1). Both flow-mediated vasodilation ($8.52\pm2.9\%$ in hemodialysis patients and $13.33\pm1.44\%$ in CKD patients) and flow-independent vasodilation (nitroglycerine mediated)($15.93\pm3.4\%$ in HD group and $17.06\pm2.02\%$ in CKD) were compromised when compared to controls(FMD $16.02\pm2.9\%$ and NMD $20.76\pm4.3\%$)($p<0.05$).FMD was significantly compromised in HD versus CKD group ($p<0.05$)but this was not the case for NMD.

Both FMD and NMD were correlated to patient's hematocrit value and to each other in both groups of patients on HD and CKD patients. They were significantly negatively correlated also with serum creatinine and PTH level (Table 2 and 3). Calcium and phosphorus levels were not statistically correlated with neither FMD nor with NMD.

Multiple linear regression analysis evaluating age, calcium, phosphorus, calcium \times phosphorus product, PTH, NMD and hematocrit value in both groups as well as dialysis duration for HD group, showed that only PTH level and patient's age were significant in all studied groups(Table 4,5).

Table1: descriptive data of studied groups.

| | HD | CKD | CONT | P |
|-------|----------------|--------------|--------------|--------|
| age | 45.38±6.48 | 45.9±5.3 | 44.83±6.36 | 0.056 |
| BUN | 99.32±22.4* | 44.6±12.9§ | 15.1±2.6° | 0.007* |
| CREAT | 11.8±2.9* | 3.22±1.13§ | 0.92±0.26° | 0.032* |
| CHOL | 167.22±29.45 | 167.8±25.7 | 163.92±23.33 | 0.067 |
| TGs | 131.35±41.61 | 126.43±30.8 | 121.44±27 | 0.342 |
| HDL | 42.24±8.6 | 43.7±9.2 | 55.9±6.6 | 0.432 |
| LDL | 104.15±23.55 | 97.62±23.9 | 84.9±16.4° | 0.017* |
| Hb | 10.7±1.73 | 11.8±0.56 | 13.8±1.95° | 0.034* |
| Hct | 26.52±4.41* | 31.25±3.7§ | 37.66±3.6° | 0.006* |
| FMD | 8.52±2.9* | 13.33±1.44§ | 16.02±2.9° | 0.000* |
| NMD | 15.93±3.4 | 17.06±2.02§ | 20.76±4.3° | 0.006* |
| CA | 9.81±1.1 | 9.46±0.68 | 10.32±1.76 | 0.196 |
| PHOS | 7.9±1.21* | 4.45±0.56 | 3.8±0.93° | 0.031* |
| CA×P | 68.94±16.91* | 42.11±6.54 | 36.14±9.22° | 0.005* |
| PTH | 306.98±112.93* | 195.63±52.6§ | 38.03±16.2° | 0.000* |

BUN :blood urea nitrogen; CREAT: creatinine: CHOL: cholesterol ; TGs: Triglycerides ;HDL :high density lipoprotein ; LDL: low density lipoprotein ;Hb: hemoglobin ;Hct: hematocrit value; FMD: flow mediated dilatation ;NMD: nitroglycerine mediated dilatation: CA: calcium;PHOS:phosphorus; CA×P; calcium phosphorus product;PTH: parathyroid hormone.

- *P<0.05 between HD and CKD ;
- §P<0.05 between CKD and Control;
- °P<0.05 between HD and Control

Table 2:Correlation between FMD and different parameters in different groups.

| | HD | | CKD | | CONTROL | |
|------|--------|--------|--------|--------|---------|--------|
| | r | P | r | P | r | P |
| NMD | 0.992 | 0.000* | 0.875 | 0.000* | 0.987 | 0.000* |
| Cr | -0.990 | 0.007* | -0.859 | 0.001* | -0.866 | 0.001* |
| Hct | 0.987 | 0.042* | 0.992 | 0.031* | 0.876 | 0.041* |
| CA | 0.048 | 0.774 | 0.185 | 0.329 | 0.135 | 0.484 |
| PHOS | -0.045 | 0.078 | -0.124 | 0.514 | -0.139 | 0.51 |
| CA×P | -0.033 | 0.839 | -0.019 | 0.921 | -0.059 | 0.756 |
| PTH | -0.904 | 0.000* | -0.968 | 0.016* | 0.078 | 0.681 |

NMD: nitroglycerine mediated dilatation ;Cr: creatinine; Hct: hematocrit: CA: calcium; PHOS:phosphorus; CA×P; calcium phosphorus product ;PTH: parathyroid hormone.. * P<0.05

Table3: Correlation between NMD and different parameters in different groups.

| | HD | | CKD | | CONTROL | |
|------|--------|--------|--------|--------|---------|--------|
| | r | P | r | P | r | P |
| FMD | 0.992 | 0.000* | 0.875 | 0.000* | 0.987 | 0.000* |
| Cr | -0.994 | 0.035* | -0.853 | 0.032* | -0.986 | 0.043* |
| Hct | 0.864 | 0.047* | 0.998 | 0.022* | 0.769 | 0.006* |
| CA | 0.048 | 0.772 | 0.168 | 0.374 | 0.078 | 0.686 |
| PHOS | -0.052 | 0.749 | -0.102 | 0.592 | -0.089 | 0.641 |
| CA×P | -0.042 | 0.795 | -0.101 | 0.594 | -0.030 | 0.874 |
| PTH | -0.864 | 0.000* | -0.842 | 0.000* | 0.058 | 0.761 |

NMD: nitroglycerine mediated dilatation ;Cr: creatinine; Hct: hematocrit; CA: calcium; PHOS:phosphorus; CA×P; calcium phosphorus product ;PTH: parathyroid hormone.. * P<0.05

Table 4:Linear regression analysis of FMD and NMD in hemodialysis patients.

| | FMD | | | NMD | | |
|-------------------|--------|--------|--------|--------|--------|--------|
| | B | t | P | B | t | P |
| constant | --- | 35.192 | 0.000* | | 26.316 | 0.000* |
| age | -0.525 | 5.75- | 0.000* | -0.446 | -3.014 | 0.006* |
| Dialysis duration | -0.030 | -0.825 | 0.418 | -0.59 | -1.018 | 0.319 |
| CA | 0.106 | 1.523 | 0.141 | 0.128 | 1.086 | 0.289 |
| P | 0.252 | 1.796 | 0.086 | 0.313 | 1.318 | 0.2 |
| CA×P | -0.016 | -1.147 | 0.263 | -0.033 | 1.457- | 0.158 |
| PTH | -0.255 | -8.002 | 0.000* | -0.144 | -2.794 | 0.01* |

Table 5: Linear regression analysis of FMD and NMD in CKD patients.

| | FMD | | | NMD | | |
|----------|--------|---------|--------|--------|--------|--------|
| | B | t | P | B | t | P |
| constant | --- | 5.284 | 0.000* | ---- | 11.74 | 0.041* |
| Age | -0.250 | -29.527 | 0.013* | -0.992 | -29.5 | 0.001* |
| CA | -0.095 | -0.351 | 0.728 | -0.095 | -0.351 | 0.728 |
| P | -0.601 | -0.513 | 0.612 | -0.233 | -0.513 | 0.612 |
| CA×P | 0.006 | 0.303 | 0.764 | 0.279 | 0.522 | 0.606 |
| PTH | 0.254 | 0.0737 | 0.468 | 0.027 | 0.737 | 0.046* |

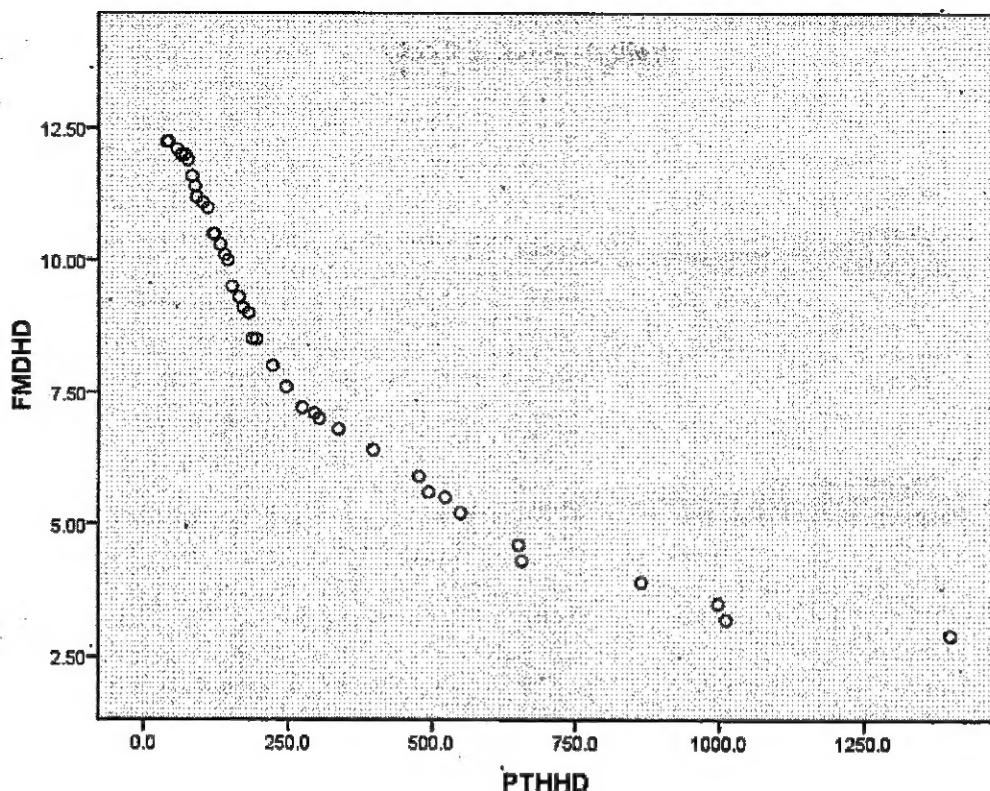


Figure 1 :Regression analysis of PTH and FMD in HD group.

Discussion

In adult patients with CRF and ESRD, endothelial dysfunction and impaired EDV was previously reported (Annuk *et al.*, 2001). Passauer *et al.*, 2000, further reported reduced vasodilator response to exogenous nitric oxide (NO) infusion into the brachial artery, while Cottone and colleagues 2002, reported that patients with mild-to-severe renal failure had marked alterations in the autocrine-paracrine activity of the endothelium with higher circulating levels of biochemical markers of endothelial activation, probably contributing to their high rate of atherosclerotic complications.

Disorders of mineral and bone in chronic renal disease are as well associated with an increased risk for cardiovascular calcification, morbidity and mortality (Moe *et al.*, 2006).Most studies have been performed in hemodialysis and there is less information on non-dialysis patients on the

coexistence of other risk factors (Ramos *et al.*, 2008).

Secondary hyperparathyroidism is an integral component of the uremic syndrome and is almost universal in patients with renal disease and, therefore, its possible influence on the prevalence of cardiovascular alterations is likely to be more than a coincidence(Bortotolotto *et al.*,2007). Moreover, endothelial cells have PTH receptors (Isales *et al.*,2000).

In this study we excluded patients with co-morbidities known to influence cardiovascular status as well as smokers and patients on lipid lowering medications. Also, the blood pressure was controlled and there was no difference statistically between studied groups as regard their blood pressure, that is why the effect of uncontrolled hypertension on FMD could not be assessed in our study. Having no correlation between FMD and blood

pressure values in the normal range would not necessarily exclude the possibility that those with uncontrolled hypertension would have lower FMD.

We found that flow mediated vasodilatation(FMD) as well as NMD were lowest in hemodialysis patients and this was associated with increased levels of PTH but not with calcium, phosphorus or calcium×phosphorus product confirming results of Bortotolotto *et al.*,2007. This may suggest a direct vasodilatory effect of PTH not linked to alterations in calcium and phosphate metabolism .Although other studies associated the CKD-associated calcium dysregulation in endothelial dysfunction as with Cases *et al.* ,(2002)as well as Hussein *et al.*, (2008) in pediatric group.

This reduced FMD and NMD were evidenced also in the patients with CKD on conservative treatment ruling out the contributing role of dialysers bioincompatibility .So secondary hyperparathyroidism exert its effect on vascular system through dual mechanism :direct vasodilatory effect by PTH and media/adventitia effect linked to alterations in calcium and phosphate metabolism (Bortotolotto *et al.*, 2007). Because flow mediated and endothelium-independent vasodilatation were both compromised in our patients, we can not (assert) that the endothelium was the primary target of PTH.

Uremic patients exhibit an endothelial dysfunction, even before starting dialysis, which persists and is even aggravated under dialysis treatment (Cases *et al.*,2002), this was consistent with our results. Ghiadoni *et al.*, 2004, also demonstrated that endothelial dysfunction in the brachial artery of CRF patients is more pronounced in HD patients than in CKD patients as manifested by the percentage of the FMD which was statistically different between both groups being lower in hemodialysis group.

Endothelial dysfunction predicts future coronary artery disease before atherosclerotic changes appear in arteries (Bortotolotto *et al.*,2007). Our patients had no detectable coronary artery disease but FMD was compromised and PTH levels influence this alteration, therefore these patients may have subclinical atherosclerosis as a consequence of uncontrolled hyperparathyroidism.

In our work ,the correlation between FMD as well as between NMD and different laboratory parameters in hemodialysis patients showed significant negative correlation with serum creatinine, PTH ,age of patient and hemodialysis duration as well as a positive correlation between it and HDL level and hematocrit value. Diminished endothelial function with advancing age already has been described (Moens *et al.*,2005). Bortotolotto and colleagues,2007, showed that FMD was negatively correlated with PTH and age and positively with NMD. In their work the only variable which influenced flow independent vasodi-lation was flow mediated vasodilation .We can conclude that FMD in the brachial artery is related to the severity of renal failure confirming results of Annuck *et al*, 2005. Ghiadoni *et al.*,2004 also reported that FMD was related to creatinine clearance, but Hussein *et al.*,2008, found no correlation between FMD and disease duration, GFR, nor blood pressure but was correlated with serum calcium level..

Endothelial dysfunction is considered an early marker of cardiovascular disease (Kanmycheva *et al.*,2004).We demonstrated that FMD is compromised in patients with CKD and HD patients without detectable coronary and systemic atherosclerosis and PTH influence this alteration. Therefore, it is possible that these patients developed subclinical ather-osclerosis as a consequence of uncontrolled hyperparathyroidism.'

Conclusion

Control of PTH levels in different stages of kidney disease may be part of the strategy to reduce the burden of atherosclerosis associated with CKD and PTH levels could be useful to identify patients at higher risk of future cardiovascular events.

A more large study may be required to detect level of GFR and level of PTH at which endothelial dysfuncyion start to occur.

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الاختلال الوظيفي للغشاء المبطن للأوعية الدموية و فرط إفراز الغدة الجار درقيه الثانوى فى مرضى الفشل الكلوى

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المقدمة: تعتبر أمراض القلب المؤد الرئيسي للأمراض والوفيات لدى مرضى الفشل الكلوى⁰ يمثل الاختلال الوظيفي للغشاء المبطن للأوعية الدموية عامل نديري إلزامي لتصلب الشرايين⁰ كما يمثل فرط إفراز الغدة الجار درقيه الثانوى عامل متم للتلازمة تبول الدم .

الغرض: دراسه الاختلال الوظيفي للغشاء المبطن للأوعية الدمويه فى مرضى الفشل الكلوى و علاقته بفرط إفراز الغدة الجار درقيه الثانوى.

المرضى وطريقة الفحص: اشتملت الدراسه على مجموعتان من المرضى: 40 مريض تحت العلاج بالغسيل الدموي 3 مرات اسبوعيا 4 ساعات بالجلسه و 30 مريض بالقصور الكلوى تحت العلاج التجفظى مقارنه بمجموعه ضابطه من 30 فرد مقارن في السن و الجنس⁰ لكل الأفراد تم عمل اختبار التمدد بالتدفق المتوسط(FMD) و التمدد بالجلسرین(NMD) كموسعات للشريان العضدي بالإضافة إلى التحاليل الروتينيه و اختبار الغدة الجار درقيه.

النتائج: أظهرت النتائج نقص في قدرة الشريان العضدي على التمدد بالتدفق المتوسط في مرضى الغسيل الدموي مقارنه بمرضى القصور الكلوى($9,44 \pm 1,33\%$ مقابل $8,52 \pm 2,9\%$) و كذلك في التمدد بالجلسرين($15,93 \pm 3,44\%$ مقابل $17,6 \pm 2,02\%$) كما كانت النتائج أقل في كلتا المجموعتين مقارنه با لمجموعه الضابطه ($16,02 \pm 2,9\%$) للتمدد بالتدفق المتوسط و($20,76 \pm 4,3\%$) للتمدد بالجلسرين وكان الفرق ذا دلالة إحصائيه⁰ كما أظهرت الدراسه وجود فرق إحصائي بين مرضى الغسيل الدموي و مرضى القصور الكلوى بالنسبة إلى التمدد بالتدفق المتوسط ولكن ليس للتمدد بالجلسرين . وقد وجد ارتباط سلبي ذو أهميه بين مستوى الكرياتينين و نسبة هرمون الغدة الجار درقيه لكليا أنواع التمدد .

الخلاصه: يعتبر ضبط مستوى هرمون الغدة الجار درقيه في جميع مراحل مرض القصور الكلوى جزء من الإستراتيجيه اللا زمه لتقليل مشكلات تصلب الشرايين المصاحبه لمرضى الكلى⁰ كما يمكن استخدامه للتعرف على المرضى الأكثر عرضه للتعرض لأمراض القلب.